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Can Postexposure Vaccination against Smallpox Succeed?

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What can be achieved by the vaccination of individuals exposed to smallpox virus after release of the virus by bioterrorists? There exist several past sources of information on postexposure vaccination failures from which it may be inferred that prompt vaccination of contacts (i.e., individuals exposed to smallpox) often prevented smallpox altogether, that revaccination of previously vaccinated individuals at any time during the first week of the incubation period was largely protective, and that revaccination done even as late as the second week of the incubation period attenuated disease and prevented most deaths. Primary vaccination done within 4 days of exposure was also usually protective at least from serious illness. Modern contingency planning against the release of smallpox virus during a bioterrorist attack should therefore include the capacity for prompt tracing and (re)vaccination of all contacts. Because a growing majority of the population has never before been vaccinated against smallpox and, so, may be unreachable within 4 days, anticipatory vaccination of sections of the populations of potential target countries should be considered if the bioterrorist threat intensifies.

Edward Jenner introduced vaccination in 1796, and, by 1800, he and his associates had already gathered evidence from several thousand subjects to show that inoculation with cowpox protected against subsequent challenge by variolation, thereby confirming the findings of his original experiment on James Phipps [1, 2]. Within a few decades, Jenner's insight had been further substantiated by a multitude of individual clinical observations that indicated that previously vaccinated people were largely protected against natural exposure to smallpox. The following evidence, for example, was given, in 1857, to the Royal Commission on Vaccination (London, United Kingdom) by W. Allison, Professor Emeritus of Medicine at Edinburgh University (Edinburgh, Scotland):

> The question is not how many vaccinated persons never take smallpox, but how many vaccinated persons are fully exposed to the contagion of smallpox and escape without any disease; our assertion is that…the modified smallpox, which is the worst thing that need be apprehended in a duly vaccinated person from the poison of smallpox, is nearly devoid of danger. [3, p. 119 of the Appendix]

There remained a second question, however, that was less open to experimental proof: could vaccination after exposure to smallpox protect? Only gradually did time and circumstances allow that question to be explored, although some early evidence is to be found in John Cross's article "History of the Variolous Epidemic which occurred in Norwich in the Year 1819" [4]. Cross refers to the action taken by the mayor of the town of Thetford (near Norwich, United Kingdom):

> An individual falling down with the smallpox in June 1819 [general] vaccination was immediately determined on. The parish officers visited every house, made a list of all those liable to the contagion, and announced the hour on the following morning at which all those requiring it might be vaccinated. About 200 were vaccinated, most of them in the course of two days, and smallpox extended only to eight or ten persons, all of whom survived. [4, p. 130]

Records of the widespread European smallpox epidemic of the early 1870s show that, by that period, such postexposure vaccination was being practiced widely [5]. Postexposure prophylaxis was also embodied in the English Vaccination Acts of 1867 and 1871, which stated the following:

Received 12 November 2002; revised 10 January 2003; electronically published 18 February 2003.

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Clinical Infectious Diseases 2003; 36:622–9

1058-4838/2003/3605-0013$15.00

> As it is by Vaccination that the spread of Small-Pox can most effectually be prevented, Boards of Guardians, as soon as any case of that disease is brought into or occurs in their respective Unions or Parishes, should see that measures are promptly taken to secure, as far as necessary, the Vaccination (or, as the case may be, Re-Vaccination) of all such persons as are especially exposed to the danger of the infection. [6, pp. 139 and 140]

This legislation from the mid-Victorian era contains both (1) the assertion that the prompt vaccination of "persons especially exposed" to smallpox virus will generally stop the spread of disease, and (2) an acknowledgment that temporary assistance and extra remuneration sometimes needed to be given to the vaccination officers to assist the speedy discovery of cases.

We may conclude from the previous examples that, by the second half of the 19th century, it was generally believed that timely postexposure vaccination could protect from, or at least modify the severity of, smallpox. Most of the detailed information that we have about the outcome of vaccination in the face of smallpox outbreaks was recorded in the same era. These data are, however, selective, and they mostly pertain to patients for whom postexposure vaccination failed to provide protection and who then found themselves in the care of physicians with a special interest in smallpox. As regards the *successes* of postexposure prophylaxis, the total number of people vaccinated after exposure seems not to have been recorded; therefore, although the efficacy of postexposure vaccination in preventing and attenuating disease can be inferred, it cannot be quantified in a way that allows statistical analysis.

A century later, the World Health Organization Global Smallpox Eradication Programme in India and Pakistan did include some quantitative studies involving families and households (as summarized by Fenner et al. [7]). These studies compared the outcomes among household smallpox contacts who were vaccinated after exposure with the outcomes among household smallpox contacts who were not vaccinated after exposure. Overall, cases of smallpox occurred among 31 (24.0%) of 129 close contacts who were vaccinated after exposure, and cases of smallpox also occurred among 136 (28.3%) of 481 close contacts who were not vaccinated after exposure. However, these results lack important detail regarding the timeliness of postexposure vaccination and the history of previous vaccination, and they may include findings for many individuals who were vaccinated too late for any benefit to be expected, as well as bias in the distribution of individuals who were vaccinated. In a study in which vaccination was known not to have been delayed, only 1 (1.9%) of 53 people who were exposed to smallpox and were vaccinated within 7 days of exposure developed smallpox [8]. In another study, performed in Madras, India, in 1960, smallpox contacts (i.e., individuals exposed to smallpox) were treated with a combination of vaccine and vaccinia immunoglobulin and were compared with other individuals who were similarly exposed to smallpox but were not treated [9]. Twenty-one cases occurred among the 379 untreated control subjects, whereas among the treated group of 326 patients, only 5 patients had smallpox (4 of whom were vaccinated >7 days after exposure). This represents an ~70% reduction in the incidence of smallpox [9].

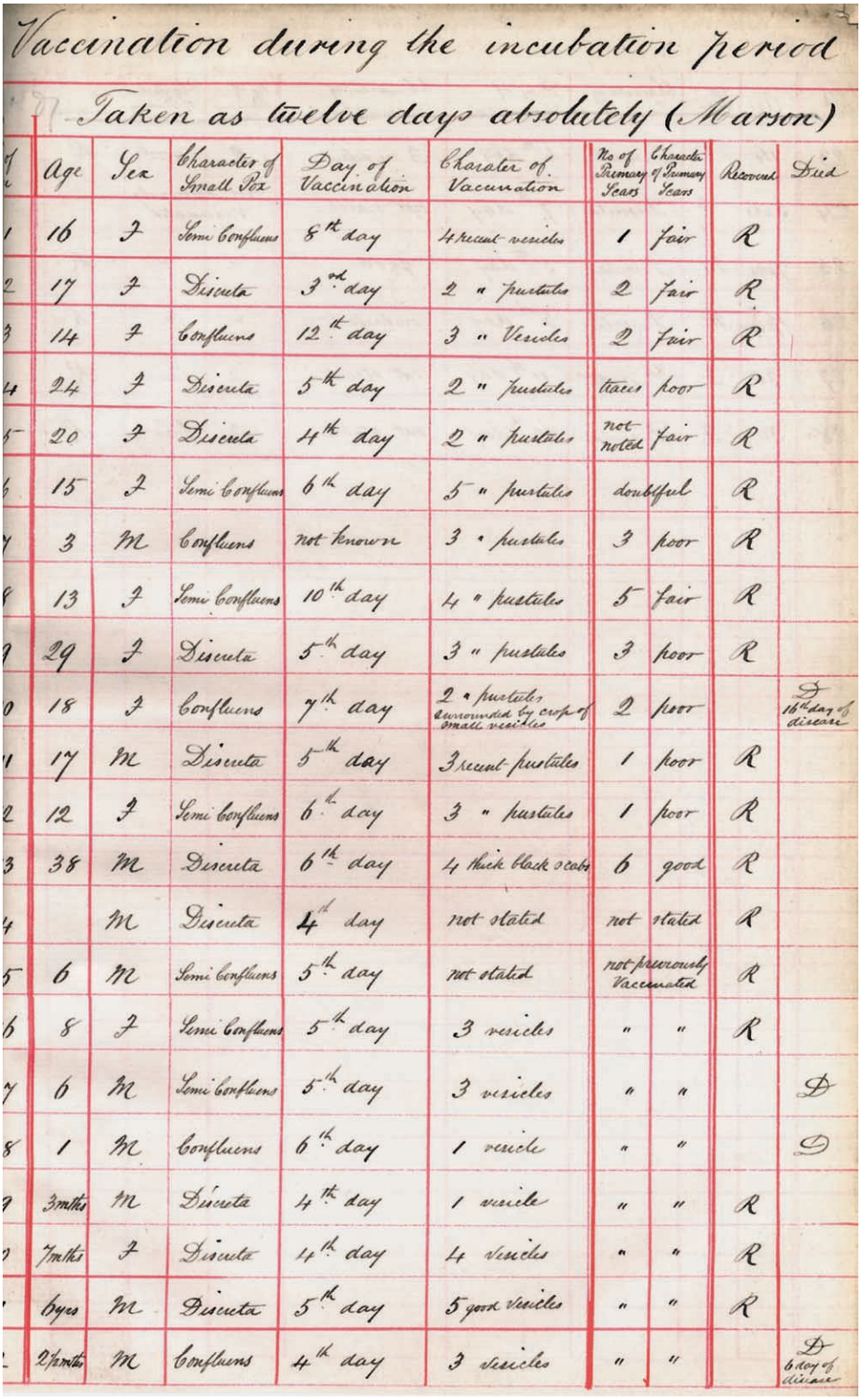
With smallpox eradicated for >20 years now, it is impossible to formally investigate the efficacy of postexposure vaccination. However, the existing data appear to show that postexposure vaccination has been beneficial to some degree. Some of the clinical observations regarding failure associated with postexposure vaccination, although they originated a century or more ago, are also sufficiently detailed to indicate when prophylaxis might be expected to work best. The purpose of the present article, therefore, is to derive from these historical data some measure of this benefit and to compare the effectiveness of the use of postexposure vaccination for previously vaccinated individuals with that for individuals who were never previously vaccinated.

Until the present threat of bioterrorism became widely appreciated, this study might have seemed academic. However, interest in smallpox vaccination has quickened since 2002, and historical data can usefully contribute to the current debate about the reintroduction of routine smallpox vaccination [10]. If postexposure vaccination can protect against release of the smallpox virus by bioterrorists, it is a possible alternative to the vaccination of whole populations in advance of a bioterrorist attack, as well as being an adjunct to any preexposure program of vaccination that might be chosen. These are sufficient reasons to review the available British records on the subject, and they might justify a similar review of, for instance, the historical French, German, and American literature.

METHODS

Data have been culled from 4 British sources. The first data source is the work of William Hanna, who, 10 years after the 1902–1903 smallpox epidemic in Liverpool, United Kingdom, analyzed and published his observations regarding patients for whom he had been caring and who had been vaccinated after having been exposed to smallpox [11, 12]. The second source, recently found among Victorian papers on smallpox in the library of the Central Public Health Laboratory (Colindale, London, United Kingdom) provides similar data (figure 1) [13]. There is no indication of the provenance or date of this second source, but these anonymous observations are meticulous and can be reconciled and compared with those of Hanna.

George Birdwood, who is quoted in Hanna's book as having presented his work to the London Clinical Society in 1878, is

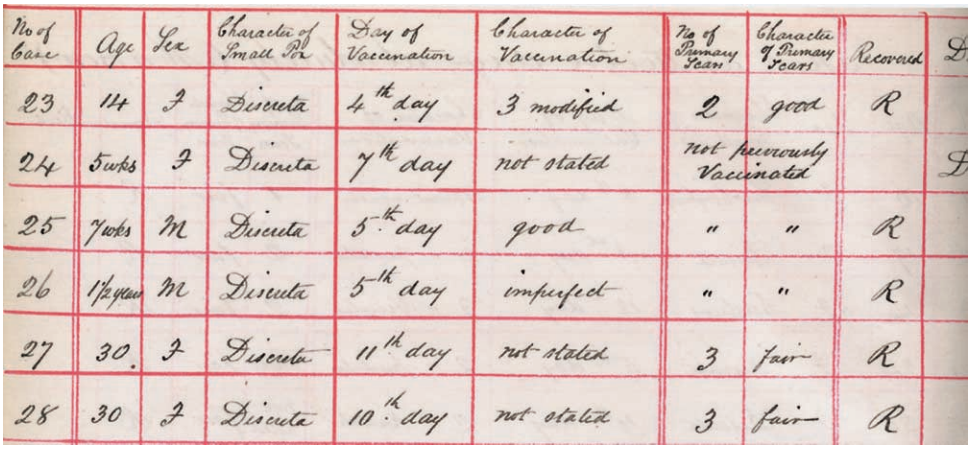


Vaccination during the incubation period

Taken as twelve days absolutely (Marson)

	Age	Sex	Character of Small Pox	Day of Vaccination	Charater of Vaccination	No of Primary Scars	Character of Primary Scars	Recovered	Died
1	16	F	Semi Confluens	8th day	4 recent vesicles	1	fair	R	
2	17	F	Discreta	3rd day	2 " pustules	2	fair	R	
3	14	F	Confluens	12th day	3 " Vesicles	2	fair	R	
4	24	F	Discreta	5th day	2 " pustules	traces	poor	R	
5	20	F	Discreta	4th day	2 " pustules	not noted	fair	R	
6	15	F	Semi Confluens	6th day	5 " pustules	doubtful		R	
7	3	M	Confluens	not known	3 " pustules	3	poor	R	
8	13	F	Semi Confluens	10th day	4 " pustules	5	fair	R	
9	29	F	Discreta	5th day	3 " pustules	3	poor	R	
10	18	F	Confluens	7th day	2 " pustules surrounded by crop of small vesicles	2	poor		D 16th day of disease
11	17	M	Discreta	5th day	3 recent pustules	1	poor	R	
12	12	F	Semi Confluens	6th day	3 " pustules	1	poor	R	
13	38	M	Discreta	6th day	4 thick black scabs	6	good	R	
14		M	Discreta	4th day	not stated	not	stated	R	
15	6	M	Semi Confluens	5th day	not stated	not previously Vaccinated		R	
16	8	F	Semi Confluens	5th day	3 vesicles	"	"	R	
17	6	M	Semi Confluens	5th day	3 vesicles	"	"		D
18	1	M	Confluens	6th day	1 vesicle	"	"		D
19	3mths	M	Discreta	4th day	1 vesicle	"	"	R	
20	7mths	F	Discreta	4th day	4 vesicles	"	"	R	
	6yrs	M	Discreta	5th day	5 good vesicles	"	"	R	
2	2½mths	M	Confluens	4th day	3 vesicles	"	"		D 6 day of disease

Figure 1. Anonymous medical record of 28 patients who were vaccinated during the smallpox incubation period and who subsequently developed smallpox (characterized by a "discrete," "semiconfluent," or "confluent" rash) [13]. The day of vaccination appears to have been back-calculated from the observed day of onset, with "the incubation period taken as twelve days absolutely."



No of Case	Age	Sex	Character of Small Pox	Day of Vaccination	Character of Vaccination	No of Primary Scars	Character of Primary Scars	Recovered	D
23	11	F	Discreta	4th day	3 modified	2	good	R	
24	5 wks	F	Discreta	7th day	not stated	not previously Vaccinated			D
25	7 wks	M	Discreta	5th day	good	"	"	R	
26	1½ year	M	Discreta	5th day	imperfect	"	"	R	
27	30	F	Discreta	11th day	not stated	3	fair	R	
28	30	F	Discreta	10th day	not stated	3	fair	R	

Figure 1. *(Continued)*

a third author whose data on the severity of smallpox after postexposure vaccination are presented. Birdwood was a physician of the London Metropolitan Asylum Board Smallpox Hospitals in the 1870s and 1880s [14]. In August 2002, an unsuccessful attempt was made to locate the record of his original presentation in the library of the Royal Society of Medicine (London, United Kingdom), which was formed from the London Clinical Society in 1907. A fourth data source is the record of postexposure vaccination failures noted by Dr. A. K. Chalmers (who was the Medical Officer of Health for Glasgow, Scotland, during the smallpox outbreak of 1901–1902) and reported by McVail [15, 16].

None of these data sets offer complete clinical details, and it is important to realize that neither do they record the total number of individuals exposed to smallpox at the time that the vaccine failures occurred. Hanna does not provide the age and sex of his patients, and he classifies the severity of smallpox in his patients as mild, moderate, and severe, whereas the anonymous medical record describes only the type of rash observed in association with each case (i.e., discrete, semiconfluent, or confluent). In the present analysis, "mild" is equated with "discrete," "moderate" is equated with "semiconfluent," and "severe" is equated with "confluent," which allows these 2 data sets to be presented in a composite table (table 1). This table relates the outcomes of the failed vaccinations to the interval between exposure and vaccination.

RESULTS

Postexposure vaccination failures among previously vaccinated patients. To relate outcomes to the timeliness of postexposure revaccination, data on cases of smallpox among individuals known to have been vaccinated previously are incorporated in table 1, which presents patient data according to the postexposure day of vaccination. There were 62 previously vaccinated patients, the ages of whom (where known) ranged from 3 to 38 years. Forty-one patients had mild smallpox, 16 had moderate smallpox, and 5 had severe smallpox. Of the 5 patients with severe smallpox, 1 patient, an 18-year-old woman who was vaccinated on day 7 after exposure, died.

Among the 11 people who were vaccinated up to 5 days after exposure, no cases of severe/confluent smallpox occurred, and only 3 such cases occurred among the 36 people who were vaccinated during the first 8 days after exposure. The history of vaccination for those 3 patients may not have been reliable. For 1 of the 3 patients (see column 8 in figure 1), the scar of previous vaccination was described as "poor."

Postexposure vaccination failures among previously unvaccinated patients. The data show that individuals were at greater risk for severe smallpox if they had not been vaccinated previously. Mild illness/discrete rash was an outcome seen exclusively among individuals vaccinated during the first week after exposure, and there were bad outcomes (i.e., confluent smallpox and/or death) for many patients who were vaccinated ⩾4 days after exposure (table 1). In all, there were 7 deaths among 39 previously unvaccinated people. On the other hand, of 7 patients who were vaccinated for the first time within 4 days after exposure, only 1 patient (a 2-month-old infant) had other than a mild case of smallpox; that patient eventually died.

Vaccination "takes" (i.e., positive vaccine reactions) among individuals exposed to smallpox. For the individuals shown in table 1 who were vaccinated >12 days after exposure, no takes were achieved either in the previously vaccinated patients or in the previously unvaccinated patients. Birdwood's data (see table 2 and data in the "Further data on the effect of timely vaccination with a take on the severity of smallpox" subsection below) also show that vaccinations with definite takes were only achieved up to day 11 of the smallpox incubation period. Thereafter, it may be assumed that postexposure vaccination could not affect outcome. However, the mitigating effect of previous

Table 1. Severity of smallpox, according to vaccination status, after the failure of postexposure vaccine prophylaxis.

Postexposure day of vaccination[a]	Patients' vaccination status and severity of illness/rash					
	Previously vaccinated			Not previously vaccinated		
	Mild/ discrete	Moderate/ semiconfluent	Severe/ confluent	Mild/ discrete	Moderate/ semiconfluent	Severe/ confluent
0	—	—	—	—	—	—
1	—	—	—	—	—	—
2	—	—	—	2	—	—
3	2	—	—	1	—	—
4	4	—	—	3	—	1[a]
5	5	—	—	4	4[a]	—
6	7	4	2	1	1	1[a]
7	5	1	1[a]	1	2	1[a]
8	4	1	—	1	2	—
9	—	—	—	—	1	1
10	1	—	1	—	—	—
11	3	—	—	—	—	1
12	2	—	1	—	—	1[a]
13	1	—	—	—	—	1
14	—	—	—	—	—	2
15	3	1	—	—	—	1
16	—	4	—	—	3	2[a]
17	3	2	—	—	—	1[a]
18	1	3	—	—	—	—
Total	41 (66.1)	16 (25.8)	5 (8.1)	13 (33.3)	13 (33.3)	13 (33.3)
Total who died	—	—	1	—	1	6

NOTE. Data are no. or no. (%) of patients. Data are a composite of data from Hanna [11] and the anonymous second source used in the present analysis [13].

[a] Estimated.

vaccination on the severity of ensuing smallpox is clearly seen when the late postexposure vaccinations in table 1 are considered separately. Among previously vaccinated patients who were revaccinated ⩾12 days after exposure, the severity of smallpox was mild/discrete for 10 patients, moderate/semiconfluent for 10, and severe/confluent for 1. Among patients without a history of previous vaccination who were vaccinated ⩾12 days after exposure, the severity of smallpox was mild/discrete for 0 patients, moderate/semiconfluent for 3, and severe/confluent for 8. No vaccine takes were achieved when vaccination was done ⩾12 days after exposure, so that only previous vaccination could have been expected to influence the outcome.

Relative success of postexposure vaccination of individuals known or assumed to have been vaccinated in the past. In the Glasgow smallpox outbreak of 1901–1902, as described by McVail [15], an estimated 400,000 people were vaccinated, including many who were assumed to have been vaccinated in the past. The 400,000 people included an unknown number of individuals, perhaps several hundred, who were vaccinated within 2 weeks after exposure to smallpox. Of the 126 individuals with smallpox who were known to have been vaccinated during that interval, there were 101 for whom the day during the incubation period when vaccination was performed was known; of these 101 patients, only 7 were vaccinated on days 0–3 (table 3). This suggests that early postexposure vaccination (i.e., vaccination on days 0–3 of the incubation period) was highly protective. (If protection were unrelated to the day during the incubation period when vaccination occurred, ~30 of the 101 patients would have been expected to have been vaccinated on days 0–3).

Further data on the effect of timely vaccination with a take on the severity of smallpox. Birdwood's data (table 2) associate the severity of smallpox with the interval between exposure and vaccination, and they show morbidity to be proportional to that interval. The patient who was vaccinated on the day of exposure had no illness, the 15 patients vaccinated 3–12 days after exposure had a discrete rash, and the 4 patients vaccinated 13–15 days after exposure had a confluent rash. The

Table 2. Severity of smallpox among and successful vaccination takes for 20 patients who were vaccinated after exposure to smallpox.

Patient(s)	Day(s) of vaccination	Quality of vaccination take(s)	Outcome		
			Illness without rash	Discrete rash	Confluent rash
1	Day of exposure	Successful	1	—	—
2–15	Between day 3 and day 11 of the incubation period	Successful	—	14	—
16	Day of onset of illness (day 12)	Doubtful	—	1	—
17 and 18	Day 13 and day 14	Doubtful	—	—	2
19 and 20	Day 14 and day 15	Unsuccessful	—	—	2

NOTE. Data are from Birdwood (see [11]). No information was given regarding whether any of the 20 patients had been previously vaccinated.

5 patients who were vaccinated after the onset of smallpox did not have a successful take, so their illnesses probably were not modified by vaccination.

DISCUSSION

The current threat from the release of smallpox virus during a bioterrorist attack is difficult to assess. However, smallpox is a singularly unpleasant and dangerous infection [17] that is transmissible from human to human. It is therefore important to establish the best means of protecting modern populations from smallpox. This might or might not entail general reintroduction of smallpox vaccination on a voluntary basis; however, in either case, there would be many individuals who, at the moment of release of smallpox during a bioterrorist attack, would be unprotected by recent or, more often, any vaccination. The protection of those individuals would have to be based on postexposure vaccination. The efficacy of this postexposure vaccination remains inadequately documented, even though it was practiced for at least 150 years, from Jenner's time up to the 1970s.

The moment of exposure to an infectious disease is often uncertain, and the natural outcome of any viral infection varies; postexposure prophylaxis is therefore rarely easy to evaluate. For smallpox, especially, conditions that would have allowed for detailed record keeping were unlikely to have prevailed while clinicians and public health officials were struggling to contain outbreaks, and the frequency, intensity, and diagnostic accuracy of reported exposures to smallpox were mostly undocumented. Consequently, the timeliness and effectiveness of vaccine prophylaxis has been impossible to quantify, mainly because the total number of individuals exposed to smallpox and thus the number of individuals who did *not* become ill thereafter were not recorded. However, the strong impression given by the present data (more so for previously vaccinated individuals than for previously unvaccinated individuals) is that disease was frequently avoided or mitigated by timely vaccination.

The aforementioned data all refer to subjects who, although vaccinated during the incubation period or early illness, became mildly to severely ill. Hanna [11] and the anonymous medical record [13] distinguish between individuals with and those without a history of previous vaccination, and this was probably the most important determinant of outcome. It is, however, a

Table 3. Number of individuals exposed to smallpox who received postexposure vaccination that failed.

Postexposure day of vaccination[a]	No. of individuals vaccinated (n = 101)
0	1
1	1
2	1
3	4
4	13
5	11
6	6
7	17
8	20
9	7
10	3
11	11
12[b]	6

NOTE. Data are from McVail [15]. No information was given regarding whether any of the 20 patients had been previously vaccinated.

[a] Day of incubation period.

[b] Day 12 was considered to be the day of onset of illness.

distinction made only by Hanna in the presentation of his data, which he published in 1913; Hanna had (presumably) a better immunological understanding than did the earlier authors. The anonymous source also provides such information, but Birdwood [11] and McVail [15] unfortunately fail to make the distinction.

The data used in the present article contain several probable biases. As already emphasized, use of postexposure vaccination may have aborted many illnesses, but these successes are not recorded. The observations probably all involve cases recorded by hospitals, and milder cases developing after postexposure vaccination may not have been diagnosed or may have been treated in the home and so may not be represented here. For both reasons, the data probably exaggerate the degree of failure of postexposure vaccination.

A surprising feature of the data is the absence of any evidence that postexposure vaccination delayed the onset of disease, and this may also be a source of bias. The lack of variability in the incubation period is, in reality, probably an artifact arising from an assumption on all 4 authors' part that the incubation for smallpox was fixed at 12 days from exposure to the onset of illness (see, for example, the heading of the anonymous medical record shown in figure 1). This led the authors to use the observed date of onset of illness to calculate the day of exposure, rather than attempt to identify the day of exposure for each case. It raises the question of how much the incubation period might actually have varied and whether it could have been lengthened by intercurrent vaccination. In fact, other Victorian authorities and more recent authorities have reported incubation periods for smallpox that vary from 10 to 14 days, with extremes of <8 days to 15 days having also been reported [7] (see the Appendix). If vaccination could lengthen the incubation period, it probably was more likely that the outcome would be an attenuated illness or even no illness at all. When postexposure vaccination failed to prevent disease, it would have seemed less effective in attenuating disease than it probably was, because the assumed date of exposure was later than the true date of exposure.

It is not recorded how many of the deaths shown in table 1 (7 deaths of previously unvaccinated individuals and 1 death of a previously vaccinated individual) were due to hemorrhagic smallpox. Vaccination may have been inadequate to prevent such cases either because, before exposure, it was remote in time or poorly done, or, after exposure, it was done too late. Some authorities (see the Appendix) believed that the hemorrhagic presentation of smallpox infection had a significantly shorter incubation period than did nonhemorrhagic smallpox, so that postexposure vaccination would have had less time to act; once the coagulation defect underlying hemorrhagic disease was established, the early immune response resulting from vaccination was probably ineffectual. This emphasizes the importance of immediate and competent vaccination for achievement of the fullest possible postexposure protection.

In the past, health care teams who were intensively exposed to the smallpox virus (in terms of the dose of virus received) may have been at increased risk for severe or hemorrhagic illness. If their previous vaccination had been incompetent or if they had not been vaccinated previously, they may have been especially vulnerable to smallpox, unless they were properly (re)vaccinated before beginning work. This consideration underscores the value of identifying a cadre of already-vaccinated health care workers available to treat smallpox spread during a bioterrorist attack.

It certainly can be concluded from the 4 data sources reviewed in the present article that the earlier that postexposure vaccination was done, the more effective it was in mitigating disease. This success can be ascribed to a specific stimulus from vaccinia virus to host immunity that could both delay the onset and lessen the severity of illness. Assuming that immune plasma from vaccine recipients again becomes available, specific immunoglobulin might also be used to prevent or delay the onset of smallpox, thereby complementing vaccine prophylaxis. Specific immunoglobulin might be useful for individuals who were not previously vaccinated, as well as individuals with a relative contraindication for vaccination and individuals already exposed to smallpox for several days before they could be vaccinated. However, immunoglobulin might also be found to act against the vaccine, leading to poorer vaccination takes. In this case, the prophylaxis of choice for previously unvaccinated individuals might be vaccine alone (for individuals seen within 3–4 days of exposure) or immunoglobulin plus an antiviral (for those seen later after exposure). If an acceptable antiviral treatment is found, it could add to the range of options for postexposure prophylaxis when it is too late for vaccination alone to be effective or when it is contraindicated. Although antivirals might be most effective when given earlier after exposure, they would then negate the effect of vaccination at the time when that procedure was most likely to succeed.

Although all the data considered here are flawed, it can be seen from this review that individuals vaccinated soonest after exposure to smallpox had the best outcome, regardless of whether they had been vaccinated previously. Furthermore, individuals who were previously vaccinated fared better than did individuals who were not vaccinated previously, and, for those revaccinated during the first week of the incubation period, recovery was very likely, even if smallpox supervened. For previously unvaccinated individuals, by contrast, only vaccination during the first 3 days of the incubation period limited any subsequent disease to a mild illness with a discrete rash.

The overall impression is that at ⩾4 days after exposure to smallpox, the natural outcome is much less influenced by vaccination. Nevertheless, Dixon, in his authoritative book on

smallpox [18], concluded that "At least 50% of cases where successful primary vaccination had occurred during the first week [post-exposure] will get some vaccine-modification and reduction of severity," which implies that postexposure vaccination should be administered even to individuals exposed ⩾1 week earlier.

In conclusion, therefore, making policy for protecting populations against release of smallpox virus by bioterrorists turns on the feasibility of vaccinating everyone who is exposed within 1 week after the exposure and/or administering immunoglobulin or antiviral treatment. If the release of smallpox virus by bioterrorists was likely to be so pervasive that such timely vaccination would be logistically impossible, then that threat might make it necessary, as some authorities now propose [19], to reintroduce routine vaccination in anticipation of any release. Even this, however, would not remove the need for contingency planning for rapid postexposure vaccination of known and suspected contacts, and this would be especially urgent for those who, for whatever reason, had not been vaccinated previously.

Acknowledgements

I thank Margaret Clennett, for her librarianship, and Bharati Purohit and Barbara Nurchi, for their secretarial help.

APPENDIX

MURCHISON ON THE INCUBATION PERIOD OF SMALLPOX

In 1878, Murchison [20] reported 3 cases of smallpox with typical incubation periods of 11–13 days. He then quoted contemporary authors as follows:

> Curschman, in his recent article on variola remarks that the latent period of smallpox is not so constant as is always maintained. In cases where he had been able to fix it exactly, it had certainly been most often between ten and thirteen days, but in others it had been as long as fourteen days, or as short as from eight to ten days, while in one it was only five days. Zuelzer also found the period of incubation in certain [nine] cases of haemorrhagic smallpox to be only from six to eight days. Lastly, the fact that the incubation-period of smallpox is far from being fixed was demonstrated by the late Dr. Otto Obermeier, in a memoir containing the largest collection of observations on the latent period of smallpox with which I am acquainted. Of eighteen cases in which the actual moment of infection was determined, in 1 the incubation-period was 5 days, in 1 the incubation-period was 6 days, in 3 the incubation-period was 8 days, in 1 the incubation-period was 9 days, in 2 the incubation-period was 10 days, in 5 the incubation-period was 11 days, in 4 the incubation-period was 12 days, in 1 the incubation-period was 13 days. (Total: 18 cases). [20, pp. 239 and 240]

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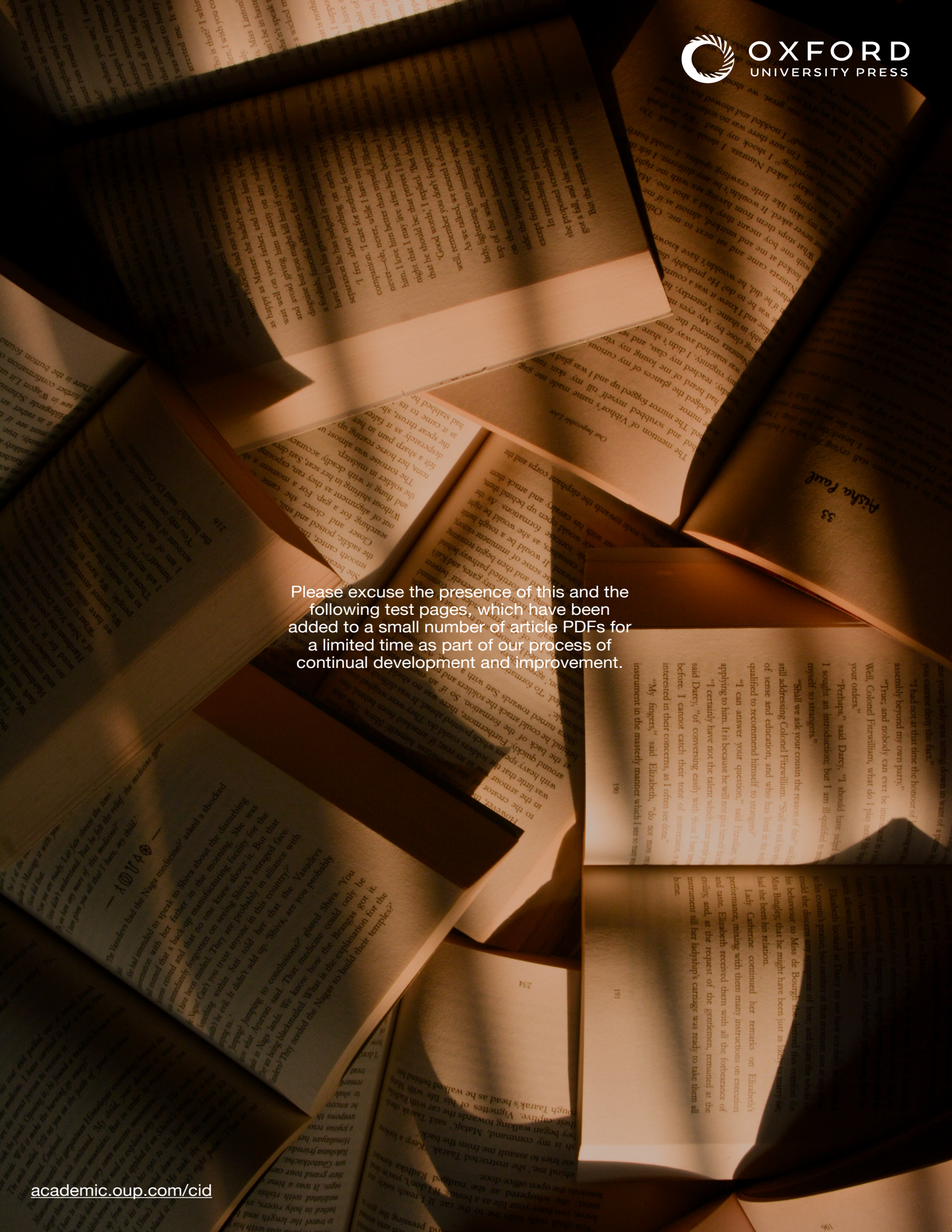

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